REMARKS

Claims 1, 2, 20, 25, 31-37, 44, 49-50, 55-57, 59-60 and 76 have been amended. Claims 7, 17, 46-47 and 77 have been canceled. Claims 5-6, 8-15, 26-27, 38, 43, 45, 53-54 and 62-75 were previously canceled without prejudice. Claims 30 and 58 were previously withdrawn. Subsequent to the entry of the present amendment, claims 1-4, 7, 16-25, 28-37, 39-42, 44, 48-52, 55-61, 76 and 78 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

I. Amendment to the Claims

Claims 1, 20, 25, 31-37, 44, 49-50, 55-57, 59-60 and 76 have been amended, in part, per the suggestion of the Office Action and to improve their form and clarity. Claims 7, 17, 46-47 and 77 have been canceled.

Claim 1 has also been amended to delete the phrase, "comprising at least 8 primers"

Claims 7 and 17 have been canceled because they have been incorporated into claims 1 and 16.

Claim 20 has been amended to delete the phrase, "substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto", and to recite that the "contiguous sequence of at least ten nucleotides and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1". Claim 20 has been amended so it does not recite an element of the claim in the negative. The amendment is supported by application and the original claim, for example, paragraphs [0043] and [0057] of the specification.

Claim 25 has been amended to improve its form and to particularly pointing out and distinctly claiming the subject matter which Applicant regards as the invention. The amendment is supported by the specification and original claims, for example, Example 1 and FIG.2 of the application.

Claims 31-37 have been amended to improve their form.

Claims 44 and 60, and dependent claims therein, have been amended to recite a method of identifying a subject at risk for autosomal dominant polycystic kidney disease (ADPKD). There is support throughout the entire application, as admitted by the Office Action on page 15.

Claims 46 has been canceled because the subject matter has been incorporated into claim 44.

Claim 47 has been canceled, it does not further limit claim 44 from which it depends.

Claims 55-57 have been amended to correct their dependency on a pending claim.

Claim 77 has been canceled because amendment of claim 76 includes the subject matter of claim 77.

No new matter has been added.

II. Regarding the Restriction Requirement

According to the Office Action, "[g]iven that claim 1 now requires that the set of eight primer pairs hybridize to flanking regions of each of the recited regions, it does not appear that claim 7 further limits claim 1 or that claim 17 further limits claim 16 (page 2 of the Office Action)".

Claims 7 and 17 have been canceled.

Also, according to the Office Action, the specification allegedly fails to provide proper antecedent basis for a deletion in SEQ ID NO: 1 at position 3336 because, "page 109 of the specification discusses a deletion referred to at G3336 in exon 13, but does not ever discuss a deletion any mutation or deletion within exon 1 or the surrounding introns, especially not the deletion at position 3336 of SEQ ID NO: 1 that is set forth in claim 20 (page 3 of the Office Action)".

The above remarks were first stated in the Office Action mailed September 22, 2003, whereby the Office Action also stated that neither the response filed on March 6, 2003, nor the Examiner Interview of September 9, 2003, was fully responsive to the prior Restriction

Requirement mailed February 3, 2003 because Applicants' election of primers and the one SNP are allegedly located on *different* exons, and therefore the elected invention is "inoperable" (page 2 of the Office Action mailed September 22, 2003).

However, in the response filed October 21, 2003, Applicants stated that the elected mutation and primers are *not* located in different exons as alleged by the Office Action. The reason for the confusion is that Table 1 of the specification lists primers based on their "genomic coordinates", while mutations which were identified in patients suffering from the disease are based on "cDNA coordinates", which is different from the "genomic coordinates". Hence, the elected single mutation at nucleotide position 3336, and the primers detecting the same, are both located in exon 1. Therefore, the elected claimed invention is "operable" and the specification provides proper "antecedent basis" for the single deletion.

III. Rejections under 35 U.S.C. §112, Second Paragraph

The following claims are rejected for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse these rejections as they apply to the pending claims and for the reasons below.

A. Rejection of claims 1-4, 7, and 17-19

According to the Office Action, "claims 1-4, 7, and 17-19 are indefinite because the claim appears to [allegedly] require that the eight primers "selectively hybridize to a flanking sequence... of each of polycystic kidney disease-associated protein-1 (PDKl) gene sequences" and it is not clear if each of the eight primers must all hybridize to each of the eight flanking regions, or if the claim intends to set forth that the set includes at least one primer that flanks each of the regions, or some other interpretation (page 4 of the Office Action)".

Claim 1, and dependent claims therein, has been amended to delete the phrase, "comprising at least 8 primers". The claim recites a set of primers that selectively hybridize to any of the eight (8) regions in SEQ ID NO:1 as set forth in the claim. The eight primers recited in the last paragraph of claim 1 are in response to the Examiner Interview of October 20, 2004 allowing for the examination of 8 primer pairs.

Accordingly, withdrawal of rejection of claims 1-4, 7, and 17-19 under 35 U.S.C. §112, second paragraph is respectfully requested.

B. Rejection of claim 7

According to the Office Action, "claim 7 is [allegedly] indefinite over the recitation "comprising a primer of claim 1" since claim 1 requires at least eight primers, and not a single primer, it is confusing what "a primer of claim 1" refers to, whether it is intended to refer to any one primer in the set required in claim 1 or whether the claim intends to refer to the entire set of primers (paragraph bridging pages 4-5)".

The rejection with regards to claim 7 is moot, as the claim has been canceled.

Accordingly, withdrawal of rejection of claim 7 under 35 U.S.C. §112, second paragraph is respectfully requested.

C. Rejection of claims 20-24

According to the Office Action (page 5):

> Claims 20-24 are [allegedly] indefinite over the recitation "wherein the nucleotide sequence corresponds to nucleotide 3336 of SEQ ID NO: 1, and wherein nucleotide 3336 is deleted" because "the nucleotide sequence" refers to the previous part of the claim which sets forth "a contiguous sequence of at least ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO: 1," and it is not clear what it means for this ten nucleotide sequence to "correspond"

> to a particular position of SEQ ID NO: 1, especially given that the claim continues by requiring that this single corresponding nucleotide is deleted. Furthermore, it is not clear what it means to require within the broadly defined ten nucleotide sequence that nucleotide "3336" is deleted. Nucleotide 3336 of SEQ ID NO: 1 is a "t", does requirement mean that there can be no "t" nucleotide in the claimed sequence. Since the claim does not clearly set forth any context within which the deletion must take place, it is indefinite as to how to identify a molecule that has the requisite deletion.

Claim 20 has been amended to recite:

> 20. An isolated polynucleotide, comprising a contiguous sequence of at least ten nucleotides and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1

Claim 20 unambiguously recites that the polynucleotide is at least ten nucleotides in length and is about 90% complementary to the region containing the mutation/deletion at nucleotide position 3336. That is, the contiguous sequence contains at least nucleotide 3335 and 337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1. Claim 20 has been also amended so it does not recite an element of the claim in the negative.

Accordingly, withdrawal of rejection of claims 20-24 under 35 U.S.C. §112, second paragraph is respectfully requested.

D. Rejection of claims 25, 28, 29, 31-37, 39-42, and 76

According to the Office Action, "claims 25, 28, 29, 31-37, 39-42, and 76 are indefinite over the recitation "said conditions" in the final line of the "contacting" step of claim 25 because this phrase lacks proper antecedent basis in the claim and it is therefore not clear which conditions are "said conditions" (page 5 of the Office Action)".

Claim 25, and dependent claims therein, has been amended to delete the phrase, "said conditions".

Accordingly, withdrawal of rejection of claims 25, 28, 29, 31-37, 39-42, and 76 under 35 U.S.C. §112, second paragraph is respectfully requested.

E. Rejection of claims 55, 56, and 57

According to the Office Action, "claims 55, 56, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because they depend directly or indirectly from a canceled base claim. See MPEP 608.0 l(n)[R-3](V). These claims were not treated in view of the prior art because they are incomplete (page 5 of the Office Action)".

Claims 55-57 have been amended to correct their dependency on claim 44, a pending claim.

Accordingly, withdrawal of rejection of claims 55, 56, and 57 under 35 U.S.C. §112, second paragraph is respectfully requested.

IV. Rejections under 35 U.S.C. §112, First Paragraph (new matter)

The following claims are rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is moot with regards to claims 7 and 17, as they have been canceled. Applicants respectfully traverse these rejections as they apply to the pending claims and for the reasons below.

A. Rejection of claims 1-4, 7 and 16-19

Claims 1-4, 7 and 16-19 are rejected because the limitation of "A set of primers, comprising at least 8 primers" in claim 1 appears to represent new matter. When this limitation

was first added to the claim in the papers received 8/19/05, no specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. The examiner identified discussion of a set of eight primer pairs (which would comprise 16 primers) at page 22 (paragraph 0045) of the specification, but no basis for a set comprising at least eight primers could be identified. Since no basis has been identified, the claims are rejected as incorporating new matter.. (page 6 of the Office Action)".

Claim 1, and dependent claims therein, has been amended to delete the phrase, "comprising at least 8 primers". The claim recites a set of primers that selectively hybridize to any of the eight (8) regions in SEQ ID NO:1 as set forth in the claim. A primer of the invention is exemplified by any of SEQ ID NOs:3-51 and 61-113, as well as primers based substantially on these primers. Hence, the eight primers recited in the last paragraph of claim 1 was in response to the Examiner Interview of October 20, 2004 allowing for 8 primer pairs to be included in examination of the claim. Thus, no new matter has been added.

Accordingly, withdrawal of rejection of claims 1-4, 7 and 16-19 under 35 U.S.C. §112, first paragraph is respectfully requested.

B. Rejection of claims 25 and 44

According to the Office Action (paragraph bridging pages 6 and 7):

[T]he language of claim [25] suggests that all of the primer pairs selected from the elected primer pairs of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 19, and SEQ ID NO: 20 would "selectively hybridize to a PKDl polynucleotide comprising SEQ ID NO: 1 and amplify a region of the PKD1 polynucleotide but not a PKDl polynucleotide homolog," but the teachings of the specification provide that only SEQ ID NO: 3 has this ability. The other primers in the elected are not disclosed as having this specificity (see Examples). Therefore, the recitation that they do have this specificity is new matter. Claim 44 has a similar problem because it also sets forth that the primer pairs have this function, and so claim 44 and the claims that depend from it are also rejected for new matter".

Claim 25 has amended as discussed above and described in the listing of the claims. The claim particularly points out that the first amplification product results from contacting the first set of primers to the sample, including primers as set forth in SEQ ID NO:3 or SEQ ID NO:5, which are PKD1-specific PKD1. See Table 1, which describes PKD1 specific primers by an asterisk (*). The second amplification product results from contacting the first amplification product with a set second set of primer pairs, including primers as set forth in SEQ ID NOs: 19, 20, 21 and 22. The second set of primer pairs represent nesting primers which are described in Table 2 of the specification. The amendments to claim 25 have support in Example 1, and Tables 1 and 2 of the specification. Thus, no new matter has been added.

Accordingly, withdrawal of rejection of claims 25 and 44 under 35 U.S.C. §112, first paragraph is respectfully requested.

V. Rejections under 35 U.S.C. §102

The following claims are rejected for allegedly being anticipated by the cited references discussed in detail below. Applicants respectfully traverse these rejections as they apply to the pending claims and for the reasons below.

A. Rejection of claims 20, 21, and 22

According to the Office Action, claims 20, 21, and 22 are allegedly anticipated by Gonczol et al. (WO 97/40165; hereinafter "Gonczol"). Gonczol allegedly discloses (page 7 of the Office Action):

> [A]n isolated nucleic acid which comprises the nucleotide sequence 5'-AGCGCGCCGGG-3' contained within the nucleic acid encoding human CMB phosphoprotein (pp) 150 (see nucleotides 3290-3300 and 5688-5698 of the sequence given in Figure 6A and B; also see figure description, p. 4). This eleven nucleotide sequences is complementary to nucleotides 3631-3642 of instant SEQ ID NO: 1, except that the "T" at position 3336 is deleted. Thus, Gonczol et al. teach an isolated polynucleotide comprising a sequence complementary to at least

ten nucleotides "substantially identical" to a nucleotide sequence of SEQ ID NO: 1, wherein the nucleotide sequence "corresponds" to nucleotide 3336 and wherein nucleotide 3336 is deleted. Gonczol et al. teach vectors and host cells comprising this sequence (p. 10, first full paragraph for example). Thus, Gonczol et al. provide nucleic acids and constructs which meet the limitations of claim 20, 21, and 22.

It is well established, that to anticipate, a single reference must inherently or expressly teach *each and every* element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, the claimed invention must be distinct from what is apparently inherent in the reference, and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980); and *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986).

First, it appears that the Office Action is rejecting the claim based on the phrase, "substantially identical". Applicants have amended claim 20 to delete the phrase, "substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto". However, to be complete, it is submitted that Gonzcol does *not* anticipate the claimed invention for the following reasons.

Gonzcol discloses two regions, nucleotides 3290-3300 and 5688-5698, which are allegedly "substantially identical" to *an* isolated polynucleotide which is at least 10 nucleotides long in SEQ ID NO:1. Claim 20 recites that the "isolated polynucleotide, comprising a contiguous sequence of at least ten nucleotides and *is about 90% complementary* to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1 (emphasis added)". As such, Gonzcol may disclose a "substantially identical" nucleotide complementary to *a* ten nucleotide region of SEQ ID NO:1, but nucleotides 3290-3300 and 5688-5698 are *not* "about 90% complementary" to *the* ten nucleotide region surrounding and containing the 3336 deletion of SEQ ID NO:1. Thus, Gonzcol

does *not* anticipate the claims because Gonzcol does *not* disclose *each and every* element of the claimed invention.

Accordingly, withdrawal of rejection of claims 20, 21, and 22 under 35 U.S.C. §102 is respectfully requested.

B. Rejection of claims 20, 23, and 24

According to the Office Action, claims 20, 23, and 24 are allegedly anticipated by Brennan (US 5474796; hereinafter "Brennan"). Brennan allegedly discloses "an array, which is a solid matrix, having thereupon every possible 10-mer nucleic acid in a separate position on the array. Thus, Brennan provides each possible isolated polynucleotide of ten nucleotides in length, including any that are within the scope of instant claim 20. With regard to claim 23, these nucleic acids are all immobilized on a solid matrix, and with regard to claim 24, there are a plurality of nucleic acids on the solid matrix which meet the limitations of claim 20 (page 8 of the Office Action)".

Again, claim 20 has been amended to delete the phrase, "substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto". Claim 20 recites that the "isolated polynucleotide, comprising a contiguous sequence of at least ten nucleotides and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1".

Brennan does *not* anticipate the claimed invention because the general teachings of Brennan would not have enabled one skilled in the art to practice the specific elements of the claimed invention without undue experimentation. In order to anticipate an invention under 35 U.S.C. §102, a prior art reference must contain an enabling disclosure, such that one skilled in the art could make and use the described invention without further experimentation. MPEP §2121.01. Brennan is non-enabling because Brennan does not teach primers which detect a

mutation/deletion in a PKD1 gene. Brennan discloses a method of producing large, dense arrays of solid phase bound reactants in reproducible and rapid manner (Abstract; and col. 2, lines 5-7 of Brennan). Brennan does not disclose polynucleotides which are about 90% complementary to the region containing the mutation/deletion of nucleotide position 3336 in a PKD1 polynucleotide. In contrast, the present disclosure in Example 2 describes various mutations associated in PKD1. Also see Table 3 and paragraph [0234] of the specification. Therefore, because Brennan does *not* enable making a polynucleotide which is about 90% complementary to the region containing the mutation/deletion of nucleotide position 3336 in a PKD1 polynucleotide, Brennan cannot anticipate the claimed invention.

Accordingly, withdrawal of rejection of claims 20, 23, and 24 under 35 U.S.C. §102 is respectfully requested.

C. Rejection of claims 20, 23, and 24

According to the Office Action, claims 20, 23, and 24 are allegedly anticipated by Chee et al. (US 5837832; hereinafter, "Chee"). Chee allegedly discloses (page 8 of the Office Action):

> [A]n array, which is a solid matrix, having thereupon a variety of nucleic acids, one of which is their SEQ ID NO: 183. This sequence shares 90% identity with nucleotides 3329- 3339 of instant SEQ ID NO: 1, wherein the "T" at position 3336 is deleted. nucleotides 3631-3642 of instant SEQ ID NO: 1, except that the "T" at position 3336 is deleted. Thus, Chee et al. teach an isolated polynucleotide comprising a sequence complementary to at least ten nucleotides "substantially identical" to a nucleotide sequence of SEQ ID NO: 1, wherein the nucleotide sequence "corresponds" to nucleotide 3336 and wherein nucleotide 3336 is deleted. With regard to claim 23, these nucleic acids are all immobilized on a solid matrix, and with regard to claim 24, there are a plurality of nucleic acids on the solid matrix, one of which is their SEQ ID NO: 183 (see Col. 14-16).

Chee does *not* anticipate the claimed invention because the general teachings of Chee, similar to Brennan, would not have enabled one skilled in the art to practice the specific elements

of the claimed invention without undue experimentation. MPEP §2121.01. Chee is non-enabling because Chee does not teach polynucleotides which are about 90% complementary to the region containing the mutation/deletion of nucleotide 3336 of SEQ ID NO:1. Chee discloses "DNA chips" comprising various permutations of oligonucleotides immobilized on a solid matrix. Chee also discloses SEQ ID NO:183 (GGCCCGGAGC) which is allegedly "substantially identical" to the region containing the mutation/deletion of nucleotide 3336 of SEQ ID NO:1 of the claimed invention.

First, Applicants are unclear as to why SEQ ID NO:183 is compared to "nucleotides 3631-3642 of instant SEQ ID NO: 1, except that the "T" at position 3336 is deleted" as this region does not contain the claimed mutation/deletion at nucleotide position 3336 of SEQ ID NO: 1. The sequence corresponding to nucleotides 3631-3642 of instant SEQ ID NO: 1 is: CGCGCGCTGCCT. Even though claim 20 has been amended to delete the phrase, "substantially identical", SEQ ID NO:183 of Chee (GGCCCGGAGC) is neither "substantially identical" nor is it "about 90% complementary" to the region containing the mutation/deletion of nucleotide 3336 of SEQ ID NO:1 of the claimed invention.

Still, Chee does not disclose the use of these arrays and affixed primers which are about 90% complementary to the region containing the mutation/deletion of nucleotide 3336 of a PKD1 polynucleotide. As discussed above, the present disclosure in Example 2 describes various mutations in PKD1. Also see Table 3 and paragraph [0234] of the specification. Therefore, because Chee does *not* enable the skilled artisan to make a polynucleotide which is about 90% complementary to the region containing the mutation/deletion of nucleotide 3336 of SEQ ID NO:1, Chee cannot anticipate the claimed invention.

Therefore, because Chee does *not* enable any polynucleotide regions associated with ADPKD, Chee cannot anticipate the claimed invention.

Accordingly, withdrawal of rejection of claims 20, 23, and 24 under 35 U.S.C. §102 is respectfully requested.

VI. Rejections under 35 U.S.C. §112, First Paragraph (written description)

The following claims are rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is moot with regards to claims 7 and 17 as they have been canceled. Applicants respectfully traverse these rejections as they apply to the pending claims and for the reasons below.

A. Rejection of claims 1-4, 7, and 16-19

According to the Office Action, claims 1-4, 7, and 16-19 are rejected because (emphasis added; pages 9 and 10):

> Independent claim 1 ….requires that the primers comprise a 5' region which can hybridize to both PKD1 and "a PKD1 gene homolog" and a 3' region that selectively hybridizes to a PKD1 gene sequence but not to the gene homolog. Instant claim 1, as elected, requires instant SEQ ID NO: 3, 4, 19, and 20. Of these, only instant SEQ ID NO: 3 is identified in the specification as being a "PKD1 specific primer" (see Table 1, p. 103 of the specification). The specification identifies eight additional primers as being PKD1 specific, that is instant SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18.
>
> The scope of the claim is very broad with regard to the identity of the required eight primers that are contain portions that hybridize to PKD1 but not to PKD1 homologues, since of these 8 only one is identified by the recited SEQ ID NO: 1. These primers can possibly be chosen from anywhere within the disclosed 53,522 nucleotide sequence of instant SEQ ID NO: 1, but there is no guidance as to which regions are unique to PKD1 relative to the undefined homologs.
>
> [Further], the specification provides an over five kilobase nucleic acid sequence (instant SEQ ID NO: 1) which it teaches is a "wild-type" PKDl gene sequence

> (paragraph |0054). The specification does not provide the nucleic acid sequence of any "PKDl gene homolog" nor does the specification provide a definition of what structural features identify such a homolog. The specification teaches that the sequence of PKDl was aligned with that of two homologues present in GenBank record AC002039 (1)0223). This record does not annotate the presence of the homologues. The identity of the nucleic acid sequence of PKDl homologues is essential for the practice of the claimed invention, as one would need the nucleic acid sequence of these homologues to in order to select additional members of the claimed set of oligonucleotide primers. Roelfsema et al. [and] the post-filing date art teaches that there are at least four additional homolog sequences of PKDl on human chromosome 16p 13.1, all with a high degree of identity to SEQ ID NO: 1, and that the exact number of the homologous genes as well as their structure is yet unknown (Bogdanova et al. Genomics, 2001, see first page and throughout)...
>
> Thus, the claims encompass primers which are designed to exclude the amplification of nucleic acid homolog sequences that were not described at the time the invention was made, and that are not described in the instant specification. There is no guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers (millions of possible primers within SEQ ID NO: 1) which ones would meet the functional requirements set forth by the claims, and thus could be included within the set of "at least 8" claimed primers.

Again, claim 1 has been amended to delete the phrase, "comprising at least 8 primers". The claim recites a set of primers that selectively hybridize to any one of the regions in SEQ ID NO:1 as set forth in the claim. A primer of the invention is exemplified by any of SEQ ID NOs:3-51 and 61-113, as well as primers based substantially on these primers. The eight primers recited in the last paragraph of claim 1 was in response to the Examiner Interview of October 20, 2004 allowing for 8 primer pairs to be included in examination of the claim.

First, the Office Action alleges that although "[t]he specification teaches that the sequence of PKDl was aligned with that of two homologues present in GenBank record AC002039 (1)0223). This record does not annotate the presence of the homologues (page 9 of the Office Action)".

It is submitted that there is basis in the application and in the art at the time of the filing of the application for the alignment and derivation of the primers as described, for example, Example 1 states:

> [0223] A two-part strategy was used to generate and validate PKD1-specific primers that could be used to amplify the replicated portion of PKD1. The sequence of PKD1 (SEQ ID NO:1) was aligned with that of two homologues present in GenBank (Accession Number AC002039) and identified potential sequence differences. Candidate primers were designed such that the mismatches were positioned at or adjacent to the 3' end of the oligonucleotide so as to maximize their specificity for PKD1.

It is well understood to the skilled artisan that at the time of the filing of the present application, "the largest obstacle faced by researchers in completing the genetic analysis of PKD1 has been distinguishing it from a family of homologs that map elsewhere on chromosome 16 (page 1473, col.2, third paragraph of Watnick et al. (1997) *Human Molecular Genetics* 6(9):1473-1481; see paragraph [0008] of the specification. Watnick et al. 1997 also disclose that "[a]pproximately 70% of this gene, beginning with its 5' end , is duplicated in at least three other loci located more proximally on chromosome 16 (page 1473, col.2, third paragraph)". That is, the knowledge that chromosome 16 contains PKD1 homologs was well known in the art at the time of the filing of the present application. Further, Roelfsema et al. (1997) as cited by the Office Action, reiterates that disclosed by Watnick et al. 1997 (page 1044, col.2, first paragraph, second to last sentence)". Genbank Accession No. AC002039 discloses the total genomic sequence for chromosome 16. The art discloses that PKD1 homologs on chromosome 16 was known prior to the time that AC002039 was first deposited on May 1, 1997. Roelfsema et al. disclose that Germino et al. 1992 (*Genomics* 13:144-151) and the European Polycystic Kidney disease Consortium 1994 (*Cell* 77:881-894) both disclose that there was "very strong homology between the greater part of PKD1 gene and another locus (page 1044, col. 2, first paragraph)." So, even before AC002039 was first deposited into GenBank (May 1, 1997) and even though it

"does not annotate the presence of the homologues", the presence of PKD1 homologues on chromosome 16 was well known by Applicants as well as other skilled artisans.

Applicants also describe PKD1- specific primers "designed such that the mismatches were positioned at or adjacent to the 3' end of the oligonucleotide so as to maximize their specificity for PKD1" (paragraph [0223] of the specification). This also has basis in the art as Roelfsema et al. (1997) disclosed that, [o]nly the 3' end of the PKD1 gene (page 1044, col.2, first paragraph, second to last sentence)". Hence, Applicants strategy of alignment by using the genomic structure of the PKD1 gene (SEQ ID NO:1) with homologs present in Genbank Accession No. AC002039 to identify potential sequence differences has clear basis in the art. See also Figure 1; SEQ ID NO:1; GenBank Accession No. L39891, paragraph [0037] of the specification.

The Office Action also alleges that "[t]he identity of the nucleic acid sequence of PKDl homologues is essential for the practice of the claimed invention, as one would need the nucleic acid sequence of these homologues to in order to select additional members of the claimed set of oligonucleotide primers (page 10 of the Office Action)".

It is submitted that based on the above discussion, the skilled artisan would understand that PKD1 homologs reside on chromosome 16 and that AC002039 by describing the entire genomic sequence of chromosome 16 would thereby contain the homolog sequence. Therefore, what the Office Action considers "essential for the practice of the claimed invention" has been disclosed in AC002039, which has been incorporated in the present invention.

The Office Action further alleges that "Roelfsema et al. [and] the post-filing date art teaches that there are at least four additional homolog sequences of PKDl on human chromosome 16p 13.1, all with a high degree of identity to SEQ ID NO: 1, and that the exact number of the homologous genes as well as their structure is yet unknown (Bogdanova et al. *Genomics*, 2001, page 10 of the Office Action)".

Again, AC002039 discloses the total genomic sequence of chromosome 16. Loftus et al. 1999 *Genomics* 60(3):295-308, referred to in AC002039, also describes the "12 Mb of DNA sequence from human chromosome 16p and 16q (Exhibit A)". Therefore, *any* PKD1 homologs which are present on chromosome 16 can be found in AC002039. Further, the application discloses the various PKD1 homologs alleged by the Office Action and disclosed in Bogdanova et al. 2001:

> ... a primer of the invention can be prepared by aligning SEQ ID NO:1 with the PKD1 gene homologs contained in GenBank Accession Nos. AC002039, AC010488, AC040158, AF320593 and AF320594 (each of which is incorporated herein by reference; see, also, Bogdanova et al., *Genomics* 74:333-341, 2001, which is incorporated herein by reference) and identifying regions having potential sequence differences, then selecting as PKD1-specific primers those sequences that match over at least about ten nucleotides and that have a mismatch at or adjacent to the 3' terminus of the matched regions (see Example 1; see, also, Phakdeekitcharoen et al., *supra*, 2000). Such primers are referred to as "PKD1-specific primers" because, while they can hybridize to a PKD1 gene and a PKD1 gene homologue, an extension product only can be generated upon hybridization to a PKD1 gene due to the mismatch of one or more nucleotides in the 3' region when the primer hybridizes to a PKD1 gene homologue. Confirmation that a selected oligonucleotide is a PKD1-specific primer can be made using methods as disclosed herein (Example 1) or otherwise known in the art. For example, a simple and straightforward method for determining that a primer is a PKD1-specific primer of the invention is to perform a primer extension or an amplification reaction using the putative PKD1-specific primer and templates including a PKD1 gene sequence and PKD1 gene homolog sequences, and detecting a single extension product or amplification product generated from the PKD1 gene template, but not the PKD1 gene homolog templates. Sequences identified as PKD1-specific primers using this or another method can be confirmed by performing various control experiments as described by Watnick et al. (*supra*; 1999), for example, by comparing an amplification product obtained in a cell having a PKD1 gene with the products, if any, produced using the radiation hybrid cell line, 145.19, which lacks the PKD1 gene but contains PKD1 gene homologs.

Thus, based on the foregoing, Applicants submit that there is more than sufficient "guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers, [even if it is] millions… within SEQ ID NO: 1".

Also, based on MPEP §2111, "[t]he broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999)". Applicants submit that based on the knowledge available to the skilled artisan at the time of the filing of the application (discussed above and incorporated herein), the claims are consistent with the interpretation that those skilled in the art would reach. Therefore, Applicants have describe the claimed subject matter in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Accordingly, withdrawal of rejection of claims 1-4, 7 and 16-19 under 35 U.S.C. §112, first paragraph is respectfully requested.

B. Rejection of claims 20-24

According to the Office Action, claims 20-24 are "extremely broad" and:

> The claim requires that the claimed polynucleotide comprises at least ten nucleotides that are "substantially identical" to a portion of SEQ ID NO: 1. The phrase "substantially identical" is sufficiently broad so as to encompass a nucleotide sequence with any level of "substantial identity" to a ten nucleotide fragment of SEQ ID NO: 1, since "substantial" is not provided a limiting definition in the specification, it is broadly interpreted to include any level of identity, since one or two often nucleotides is substantial.
>
> Further, the claim recited [does not define] the level of complementarity required. Thus, the claim encompasses a polynucleotide with any level of complementarity to a substantially identical ten nucleotide fragment of SEQ ID NO: 1, wherein nucleotide 3336 (which is a T) is deleted.

> And the claims are broadly drawn using the claim language "comprising" which means that this broadly set forth ten nucleotide structure can be contained within any possible sequence context of any length. ...
>
> The specification further teaches a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1 (pertaining to the elected invention), so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described. However, given the limited disclosure of the specification and given the extremely broad nature of the claimed invention, it is concluded that the claimed invention is not supported with proper written description.

Again, claim 20 has been amended to delete the phrase, "substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto". Claim 20 recites that the "isolated polynucleotide, comprising a contiguous sequence of at least ten nucleotides and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1".

Hence, the claim *does* define the level of complementarity required, and even though it recites the term, "comprising", the claimed contiguous sequence of at least ten nucleotides is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1. Thus, a putative primer in this region of SEQ ID NO:1 may be any length, so long as it also is "about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1".

The Office Action also alleges that , "[t]he specification further teaches a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1, so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described (page 11 of the Office Action)".

Claim 20 has been amended to recite that the "contiguous sequence of at least ten nucleotides and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1". This mutation/deletion is associated with APDKD

and such is supported in the application, for example, paragraphs [0055], [0115], [0144], [0149], [0234] and original claims 20, 59 and 66. Also, as discussed above, the application describes methods of aligning the PKD1 sequence with PKD1 homologs to identify regions that have potential differences. Thus, the skilled artisan can identify and determine a primer polynucleotide having about 90% complementary to the 3336 region of PKD1 as compared to PKD1 homologs, whether it be 2, 4, 6 or more homologs. Therefore, there is proper written description for the claimed invention in the specification.

Accordingly, withdrawal of rejection of claims 20-24 under 35 U.S.C. §112, first paragraph is respectfully requested.

VII. Rejections under 35 U.S.C. §112, First Paragraph (enablement)

The following claims are rejected for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is moot with regard to claims 7 and 17 as they have been canceled. Applicants respectfully traverse these rejections as they apply to the pending claims and for the reasons below.

A. Rejection of claims 1-4, 7, 16-19

According to the Office Action, claims 1-4, 7, 16-19 are rejected "because the specification, while being enabling for primers having SEQ ID NO: 3, 5, 8, 10, 11, 14, 16, and 17, which can be used to specifically amplify PKD1 gene having SEQ ID NO: 1 and no PKD1 gene homologs, does not reasonably provide enablement for additional primers that have this property (page 12 of the Office Action)".

With regard to claim 1, and dependent claims therein, the Office Action alleges the following (pages 13-19):

Nature of the invention and breadth of the claims (pages 13-14 of the Office Action) The scope of the claim is very broad with regard to the identity of the required eight primers that are contain portions that hybridize to PKDl but not to PKDl homologues, since of these 8 only one is identified by the recited SEQ ID NO: 1. These primers can possibly be chosen from anywhere within the disclosed 53,522 nucleotide sequence of instant SEQ ID NO: 1, but there is no guidance as to which regions are unique to PKDl relative to the undefined homologs. Further, the specification does not provide any clear definition of how much sequence difference is necessary between two molecules for one to be a "homolog" of the other, as opposed to one being a polymorphic variant of the other. Thus, for these product claims the nature of the invention depends on the ability to identify primers which meet the functional characteristics set forth in the claims.

The discussion above with regard to rejection of claim 1 for allegedly lacking a written description, is incorporated herein in its entirety. As discussed above, the application in Example 1, paragraph [0223] clearly provides that the , "[c]andidate primers were designed such that the mismatches were positioned at or adjacent to the 3' end of the oligonucleotide so as to maximize their specificity for PKD1". This strategy of identifying PKD1-specific primers is supported in Roelfsema et al. *supra,* stating that "only the 3' end of the PKD1 gene is unique (page 1044, col.2, first paragraph)". Table 1 on page 103 of the specification describes various PKD1-specific primers, including SEQ ID NO:3, 5, 8, 9, 10, 11, 14 and 16 (denoted by an asterisk, *). Further, the applications describes, and claim 1 recites, that SEQ ID NOs: 11, 18, 52 and 60 have been previously described, for example, U.S. Pat. No. 6,017,717 (SEQ ID NO:11); Watnick *et al.* 1997 (SEQ ID NO:18); Watnick et al. (1999) *Am. J. Hum. Genet.* 65:1561-1571(SEQ ID NOS:9, 10, 49 to 51, and 61- 105); Phakdeekitcharoen et al. (2000) *Kidney International* 58:1400-1412 (SEQ ID NOS: 9 -12; U.S. Pat. No. 6,071,717 (SEQ ID NO:13); and Watnick et al. (1998) *Mol. Cell* 2:247-251 (SEQ ID NO:10 and TWR2 which is similar to SEQ ID NO:12). Also, paragraph [0010] describes that the, "3' region contains at least one 3' terminal nucleotide, wherein the at least one 3' terminal nucleotide is identical to a nucleotide that is 5' and adjacent to the nucleotide sequence of the PKD1 gene to which the 5' region of the primer can hybridize, and is different from a nucleotide that is 5' and adjacent to a nucleotide sequence

of the PKD1 homolog to which the 5' region of the primer can hybridize". Thus, there is sufficient guidance because the nature of the claims, Applicants disclosure and art available at the time of the filing of the application provide sufficient guidance "as to which regions are unique to PKDl relative to the undefined homologs".

With regards to the Office Action alleging that the "specification does not provide any clear definition of how much sequence difference is necessary between two molecules for one to be a "homolog" of the other, as opposed to one being a polymorphic variant of the other".

It is submitted, that whether the 3336 mutation/deletion is a "mutation" *per se* or a "polymorphism" is not particularly relevant. However, in general, a "mutation is an "alteration in the genetic material [and] includes conversion, deletion, duplication, insertion and so forth". See http://dorakmt.tripod.com/genetics/glosgen.html; Exhibit B, page 17. A "polymorphism" is "different form of a gene …which occur during frequency-dependent selection and genetic drift". See http://dorakmt.tripod.com/genetics/glosgen.html; Exhibit B, page 20. Hence, a mutation over time can become a polymorphism, and often these two terms are used interchangeably. In fact, the definition of the term, "variation", admits to the ambiguity in the use of the terms "mutation" and "polymorphism", stating instead that a "variant" is "any genetic change". See http://dorakmt.tripod.com/genetics/glosgen.html; Exhibit B, page 27. Thus, one skilled in the art would not be able to determine whether the mutation/deletion 3336 is a polymorphism observed in a particular population, but that does not take away from the fact that it is a mutation, or "alteration in the genetic material".

Further, the application describes the PKD1 gene as set forth in SEQ ID NO:1. Also see, FIG. 1 and Accession No. L39891 describe in paragraph [0037] of the specification. As such, the skilled artisan can compare the PKD1 sequence with the PKD1 homologs on chromosome 16. Also see paragraph [0039] of the specification describing the same. As such, the present invention provides methods for one skilled in the art to identify PKD1 specific primers and using these PKD1 specific primers along with other non-PKD1 specific primers to detect the presence

or absence of a mutation in the PKD1 gene. Therefore, Applicants submit that a "definition of how much sequence difference is necessary between two molecules for one to be a "homolog" of the other, as opposed to one being a polymorphic variant of the other" is not necessary nor relevant to practice the claimed invention.

> **Teachings in the specification and the prior art** (pages 16-17 of the Office Action)
> [In short], the claims encompass primers which are designed to exclude the amplification of nucleic acid homolog sequences that were not described at the time the invention was made, and that are not described in the instant specification. There is no guidance in the specification as to how to look at instant SEQ ID NO: 1 and to select, of all of the possible primers (millions of possible primers within SEQ ID NO: 1) which ones would meet the functional requirements set forth by the claims, and thus could be included within the set of "at least 8" claimed primers.

The discussion above pertaining to the written description rejection of claim 1 is incorporated herein.

Also, MPEP §2164.03 establishes that:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention.

Example 1 of the present application describes methods of identifying PKD1-specific primers by aligning PKD1 (SEQ ID NO:1) with PKD1 homologs on chromosome 16 (GenBank Accession no. AC002039). The results of which are shown in Table 1 (page 103 of the specification). Table 1 describes that at least SEQ ID NO:3, 5, 8, 10, 11, 14 and 16 are PKD1-specific primers identified using this method. Thus, Applicants disclosure alone provides "teaches exactly how to make or use the invention".

Still, MPEP §2164.03 also establishes that:

> The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

There are many publications relating to the area of ADPKD and known mutations in the PKD1 gene. For example, Phakdeekitcharoen et al. 2001 *American Society Nephrology* 12:955-963 (Exhibit C), which is based, in part, on the present application, describes that the Cardiff Human Gene Mutation Database has a complete listing of published PKD1 mutations (page 957, col.1, first paragraph). Additionally, the European Polycystic Kidney Disease Consortium was and continues to be isolating various PKD1 mutations starting since about 1994. Their work has been cited in many papers relating to detection of PKD1 mutations or the study of such mutations in ADPKD. MPEP §2164.03 states that the "more predictable the art is, the less information needs to be explicitly stated in the specification". Since, the art relating to mutations of PKD1 is many, the skilled artisan would look to the art in addition to Applicants disclosure for guidance.

Lastly, MPEP §2164.03 establishes that:

> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. In re Vickers, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); In re Cook, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971).

It is submitted, that Applicants disclosure only need to provide sufficient guidance such that one skilled in the art can make and use the invention as claimed. Based on the foregoing art discussion, the skilled artisan would not look to Applicants disclosure to provide for "every operable species".

Quantity of experimentation (pages 18-19 of the Office Action)
The quantity of experimentation required to practice the claimed invention, given the high degree of unpredictability in this art area is enormous. For the claims drawn to primer pairs, in order to practice the invention, one would have to undertake substantial trial and error experimentation to determine which possible primers, other than those comprising the SEQ ID NO: specifically given in the specification, would meet the functional requirements set forth in the claims. This would involve the synthesis of primers, but also extensive experimentation to Determine if the synthesized primers are specific to PKD1 and not to PKD1 homologs. Given the fact that there is no clear disclosure of what structural features define the PKD1 homologs in the specification, nor any requirement which indicates how much sequences have to differ from instant SEQ ID NO: 1 to be considered a homolog, and the disclosure in the prior and post filing date art that there are at least six different homologs but maybe more which are unidentified, this work would require extensive experimentation.

MPEP §2164.06 states that, "an extended period of experimentation may not be undue *if the skilled artisan is given sufficient direction or guidance*." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)." [Further,] *the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). [In brief], *time and difficulty of experiments are not determinative if they are merely routine*. In re Wands, *supra*.

It is submitted, that the art and Applicants disclosure provide sufficient guidance that the amount of experimentation is *not* "enormous" as alleged; and even if "enormous", it is *not* undue as the tests/experiments are "merely routine [and] the specification ... provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". In re Wands, *supra*. Example 1 of the present application describes the identification of PKD1 specific primers by aligning the PKD1 sequence with the PKD1 homologs. Example 1 also describes particular methods (e.g., primer sequences, annealing temperatures, extension times)

for each amplification step. So, the level of experimentation is "routine" and not anymore burdensome or undue than any other method whereby the skilled artisan has to make gene specific primers to PCR amplify a region of that gene using various conditions for amplification.

Accordingly, withdrawal of rejection of claims 1-4, 7, 16-19 under 35 U.S.C. §112, first paragraph is respectfully requested.

B. Rejection of claims 20-24, 28-37, 39-42, 44, 46-52, 55-61, and 76-78

Claims 20-24, 28-37, 39-42, 44, 46-52, 55-61, and 76-78 are rejected for allegedly not complying with the enablement requirement as stated below. This rejection includes rejection of composition claim 20, and dependent claims therein; and methods claims 25, 44 and 60, and dependent claims therein. For clarity, the two groups of claims will be addressed separately below. Also, the rejection is moot with regards to claims 46-47 and 77 as they have been canceled. Applicants respectfully traverse the rejection as it applies to the pending claims.

1) Rejection of claim 20 and dependent claims therein

With regard to claim 20, and dependent claims therein, the Office Action alleges the following (pages 13-19):

> **Nature of the invention and breadth of the claims** (page 14 of the Office Action)
> Independent claim 20… The phrase "substantially identical" is sufficiently broad so as to encompass a nucleotide sequence with any level of "substantial identity" to a ten nucleotide fragment of SEQ ID NO: 1, with any level of complementarity…

Claim 20 has been amended to recite that the "contiguous sequence of at least ten nucleotides and is about 90% complementary to at least nucleotide 3335 and 3337 of a PKD1 polynucleotide as set forth in SEQ ID NO:1". Thus, the claimed polynucleotide does *not* encompass a polynucleotide with *any* level of complementarity, rather the

polynucleotide is as "about 90% complementary" the region containing the 3336 mutation/deletion.

> **Teachings in the specification and the prior art** (page 17-18 of the Office Action)
> The specification describes instant SEQ ID NO: 1, and therefore fragments consisting of instant SEQ ID NO: 1 are described. The specification further teaches a deletion of a single nucleotide from position 3336 of SEQ ID NO: 1 (pertaining to the elected invention), so nucleotide fragments that consist of fragments of instant SEQ ID NO: 1 except that the nucleotide at position 3336 is deleted are also described. However, given the limited disclosure of the specification and given the extremely broad nature of the claimed invention, it is concluded that the claimed invention is not supported with proper *written description* (emphasis added).

This rejection appears to be substantially similar to the written description rejection of claim 20, and dependent claims therein. See paragraph 14, page 11 of the Office Action, and section **VI B** of this response. The detail discussion in section **VI B** is herein incorporated in its entirety. Claim 20 is limited to those "contiguous nucleotides" which are "about 90% complementary" to the region encompassing the 3336 mutation/deletion. Claim 20 is therefore not "extremely broad" and is fully supported by the application and original claims, for example, paragraphs [0055], [0115], [0144], [0149], [0234] and original claims 20, 59 and 66.

> **Quantity of experimentation** (page 19 of the Office Action)
> For claims 20-24, the use of the claimed invention would require extensive and entirely unpredictable work to determine if an association exists between the deletion at position 3336 of SEQ ID NO: 1 and any relevant phenotype, though the claims do not require such a use, the use of a molecule which comprises this deletion would require such knowledge.

In brief, the Office Action alleges that there is no correlation as between the mutation/deletion 3336 and the phenotype, or ADPKD. It is submitted that

this mutation *is* associated with ADPKD. Example 2 of the present application describes studies using ADPKD affected members of 47 Asian families. The identification of the mutations in Table 3 are from the same ADPKD affected individuals. Also, U.S. Application 20050100898 supports that the 3336 mutation/deletion is associated with ADPKD; see Exhibit D, page 14 of 61. Thus, the skilled artisan would reasonably accept that the mutation/deletion 3336 is associated with the ADPKD.

C. Rejection of claims 25, 44 and 60, and dependent claims therein

With regard to claims 25, 44 and 60, and dependent claims therein, the Office Action alleges the following (pages 13-19):

> **Nature of the invention and breadth of the claims**
> Regarding claims 25 and those that depend from them, these claims do not recite an association with a disease, but in the nature of the method requires such a knowledge in order for the method to be "used." …The scope of these claims is also quite broad with regard a "PKD1 related disorder," encompassing disorders such as ADPKD or acquired cystic disease, as mentioned by the specification, but also any disease or disorder that has symptoms in common with these diseases, such as urinary tract infections, blood in the urine, liver and pancreatic cysts, and kidney stones.

First, only independent claims 44 and 60 were directed to a "PKD1 associated disorder". Claims 44 and 60 have been amended to recite "autosomal dominant polycystic kidney disease (ADPKD)", which amendment is clearly supported throughout the application as discussed above.

> **Teachings in the specification and the prior art**
> Regarding the method claims, the specification does teach and exemplify that it is unpredictable whether mutations or polymorphisms in the PKDl gene will be associated with disease. … Thus, of all of the possible mutations that might be identified within the regions amplified in the

> rejected method claims, it is highly unpredictable which ones will be associated with disease. The specification has not provided a single mutation within this region that appears to be prognostic of, let alone diagnostic of disease.

It is submitted, that the present application describes how to detect the presence or absence of a mutation in a PKD1 polynucleotide (claim 25) or to identify a subject with ADPKD (claims 44 and 60). Prior to Applicants disclosure genomic DNA samples could not be used to screen all PKD1 exons for mutations. Obstacles in prior methods include: 1) cross-hybridization of primers with the PKD1 homologs (paragraph [0006]); 2) inability to screen the entire PKD1 gene because the mRNA itself was too large (paragraph [0007]); 3) inability to examine exon 1 because it is separated from the rest of the gene by an intron of approximately 19 kb and is contains extremely high GC content (approximately 85%); therefore amplifying it with high fidelity was difficult (paragraph [0007]); and 5) inability to examine exon 22 because there was no effective method for DNA based analysis of PKD1 gene exon 22, since it was flanked on both ends by introns that contain lengthy polypyrimidine tracts (paragraph [0007]). Thus, methods for identifying, detecting and amplifying PKD1 fragments containing PKD1 mutations at the time of the filing of the application was difficult and cumbersome.

The present invention provides reagents (e.g., primers and PKD1 template regions) and methods to overcome the above obstacles. Table 1 and 2 of the specification describe primers and conditions of how the eight (8) regions of the PKD1 gene can be amplified, *including* exons 1 and 22; see claim 1. In short, the PKD1 polynucleotide can now be amplified from eight PKD1 templates ranging in size from 0.3 to 5.8 kb (see Table 1 and claim 1). This was not available prior to Applicants disclosure. The eight templates then allow the use of various primers provided in the present invention (Tables 1 and 2) for amplification of long and short PKD1 fragments, using a 2 amplification step method. This approach has allowed Applicants and the skilled artisan, for the first time, to evaluate samples that had previously failed to yield suitable PKD1 products.

Therefore, the primers and methods provided in the present application make is actually more predictable which mutations are found in PKD1, or are associated with ADPKD.

> **Quantity of experimentation**
> Regarding the method claims, one would have to undertake extensive studies to first identify potential mutations or polymorphisms within the amplified region, other than the single disclosed example. Whether or not such polymorphisms or mutations exist is itself highly unpredictable, and if they do exist, the location and structure of these variants is highly unpredictable. Once mutations are identified, one would have to undergo further case controlled studies in patient and control populations to determine if the variants are predictive of any disease phenotype, and if so, which of the possible "PKD1 associated disorders" are predicted by the newly discovered mutation.

Again, MPEP §2164.06 states that, "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). [In brief], *time and difficulty of experiments are not determinative if they are merely routine*. In re Wands, *supra*.

It is submitted, as discussed above, that the amount of experimentation is *not* enormous, rather it is "merely routine [and] the specification … provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". In re Wands, *supra*. Example 1 of the present application describes the identification of PKD1 specific primers by aligning the PKD1 sequence with the PKD1 homologs. Example 1 also describes particular methods (e.g., primer sequences, annealing temperatures, extension times) for each amplification step. So, the level of experimentation is "routine" and not anymore burdensome or undue than any other method whereby the skilled artisan has to make gene specific primes to PCR amplify a region of that gene. In fact, as discussed above, prior to Applicants' disclosure exons 1

and 22 were not even capable of being examined/analyzed for mutations potentially associated with the ADPKD. Hence, Applicants disclosure has made the identification, detection, analysis and evaluation of these mutations even more predictable and less cumbersome.

Thus, for all the foregoing reasons, Applicants submit that the claimed invention is enabling for persons skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Accordingly, withdrawal of rejection of claims 1-4, 7, 16-19, 20-24, 28-37, 39-42, 44, 46-52, 55-61, and 76-78 under 35 U.S.C. §112, first paragraph is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

A check in the amount of $120.00 is enclosed as payment for the One-Month Extension of Time fee. No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: October 5, 2006

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